Tigecycline Activity Tested Against Commonly Isolated Skin and Skin Structure Infection (cSSSI) Pathogens: 2009 USA Surveillance Results

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ABSTRACT

Background: Tigecycline (TIG) is approved for for treatment of cSSSI and has shown activity against key Gram-positive and -negative bacterial pathogens worldwide, including multidrug-resistant *Acinetobacter* spp., ESBL-producing Enterobacteriaceae, MRSA and VRE; pathogens frequently isolated in the APAC region.

Methods: TIG was susceptibility (S) tested by CLSI broth microdilution methods. Isolates were collected from 27 USA hospitals during 2009 and derived from patients with cSSSI. MRSA and VRE rates were 54.6 and 22.9%, respectively. ESBL rates were 8.0 and 26.6% for *E. coli* (EC) and *Klebsiella* spp. (KSP), respectively.

Results: TIG was active against *S. aureus* (SA), coagulase-negative staphylococci (CoNS) and enterococci (ESP) ($MIC_{90,}$ 0.25 mg/L for all three organisms). TIG activity was similar among MRSA and MSSA as well as among vancomycin-S and -R ESP isolates. β-haemolytic (βHS) and viridans group streptococci (VGS) were TIG-S with MIC_{90} values of 0.06 and 0.12 mg/L, respectively. Enteric bacilli were also inhibited by TIG with MIC_{90} values lowest for EC (0.25 mg/L) compared to KSP and *Enterobacter* spp. (EBS; 1 mg/L). TIG showed limited activity against *P. aeruginosa* (MIC_{90}, >4 mg/L).

Conclusion: TIG has provided a new class of antimicrobial agents to combat serious, resistant infections which continue to increase globally. This study demonstrates the continuing in vitro efficacy of TIG against isolates associated with cSSSI, including MRSA, VRE and enteric ESBL-producing strains.

INTRODUCTION

Infections of skin and skin structures (SSSI) are among the most common of community- and hospital-acquired infections and the management of complicated SSSI (cSSSI) is often compromised by the potential microbiological diversity of prevalent pathogens. In particular, cSSSIs are characterized by a fairly high prevalence of *Staphylococcus aureus*, including the emergence of methicillin-(oxacillin) resistant *S. aureus* (MRSA) in both the hospital and community settings.

Tigecycline is a glycylcycline antimicrobial agent that has demonstrated activity against key Gram-positive and -negative bacterial pathogens worldwide, including multidrug-resistant (MDR) *Acinetobacter* spp., ESBL-producing Enterobacteriaceae (ENT), methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE); pathogens frequently isolated in the Asia Pacific (APAC) region. Tigecycline was first approved by the United States (USA) Food and Drug Administration (FDA) and later by the European Medicines Agency (EMEA) as a parenteral agent for the treatment of cSSSI, intra-abdominal infections and community-acquired pneumonia (USA only).

In the present study, we evaluated the antimicrobial activity of tigecycline and comparator agents tested against clinical bacterial isolates causing cSSSI in USA medical centers in 2009.

MATERIALS AND METHODS

Organism Collection: Consecutive, non-duplicate bacterial isolates, collected in 2009 from patients with documented cSSSI in 27 USA medical centers were evaluated. Species identifications were performed by the submitting laboratories with identification confirmation performed by the central laboratory monitor (JMI Laboratories, Iowa, USA).

Antimicrobial susceptibility testing: Susceptibility testing was performed using validated broth microdilution test panels (TREK Diagnostic Systems, Inc., Ohio, USA) with cation-adjusted Mueller-Hinton broth (2 to 5% lysed horse blood added for testing *Streptococcus* spp.). Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone were considered as extended-spectrum β-lactamase (ESBL)-producing phenotypes according to CLSI criteria (M07-A8; 2009).

Tigecycline breakpoints were those recommended by the USA-FDA, which are ≤2 mg/L (susceptible) and ≥8 mg/L (resistant) for Enterobacteriaceae; ≤0.5 mg/L for staphylococci (susceptible only) and ≤0.25 mg/L for streptococci and enterococci (susceptible only). Quality control isolates and interpretive criteria used were those recommended by the CLSI (M100-S20-U; 2010).

SELECTED REFERENCES

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RESULTS

- A total of 1,941 organisms were collected from cSSSI in the USA medical centers surveyed. *S. aureus* was the most frequently isolated pathogen (1,165 strains; 60.0%), followed by β-haemolytic streptococci (212 strains; 10.9%), *Enterococcus* spp. (140 strains; 7.2%), and *E. coli* (125 strains; 6.4%).

Table 1. Antimicrobial activity of tigecycline and selected comparator agents tested against bacterial isolates causing cSSSI in USA medical centers.

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	% Susceptible[a]	% Resistant[a]
S. aureus (1,165)				
Tigecycline	0.12	0.25	100.0	-[b]
Oxacillin	2	>2	45.4	54.6
Clindamycin	≤0.25	>2	86.8	13.0
Levofloxacin	≤0.5	>4	64.0	35.2
TMP/SMX	≤0.5	≤0.5	99.0	1.0
Linezolid	2	2	100.0	0.0
Vancomycin	1	1	100.0	0.0
β-haemolytic streptococci (212)				
Tigecycline	≤0.03	0.06	100.0	-
Penicillin	≤0.015	0.03	100.0	-
Erythromycin	≤0.25	>2	68.4	25.9
Clindamycin	≤0.25	>2	85.4	14.1
Levofloxacin	1	1	99.1	0.5
Tetracycline	≤2	>8	55.2	42.9
Linezolid	1	1	100.0	-
Enterococcus spp. (140)				
Tigecycline	0.12	0.25	98.6	-
Ampicillin	≤12	>16	76.4	25.6
Levofloxacin	2	>4	55.0	44.3
Linezolid	2	2	99.3	0.7
Vancomycin	2	>16	77.1	22.9
CoNS (58)				
Tigecycline	0.12	0.25	100.0	-
Oxacillin	1	>2	34.5	65.5
Erythromycin	>2	>2	44.8	53.5
Clindamycin	≤0.25	>8	70.7	27.6
Levofloxacin	2	>4	74.1	22.4
TMP/SMX	≤0.5	>2	75.9	24.1
Linezolid	1	1	100.0	0.0
Vancomycin	1	2	100.0	0.0
Viridans group streptococci (35)				
Tigecycline	≤0.03	0.12	100.0	-
Penicillin	0.03	0.5	82.9	8.5
Cefepime	0.25	2	88.6	2.9
Clindamycin	≤0.25	>2	82.9	11.4
Levofloxacin	1	2	91.4	8.6
Linezolid	1	1	100.0	-
Vancomycin	1	1	100.0	0.0
E. coli (125)				
Tigecycline	0.12	0.25	100.0	0.0
Piperacillin/tazobactam	2	8	93.6	3.2
Ceftriaxone	≤0.25	≤0.25	92.0	8.0 (8.0)[c]
Ceftazidime	≤1	≤1	93.6	5.6 (8.0)[c]
Cefepime	≤0.12	0.25	95.2	3.2
Imipenem	0.25	0.25	100.0	0.0
Levofloxacin	≤0.5	>4	68.0	32.0
Gentamicin	≤2	>8	88.8	10.4
Amikacin	2	4	99.2	0.0
Klebsiella spp. (64)				
Tigecycline	0.25	1	98.4	0.0
Piperacillin/tazobactam	4	>64	78.1	17.2
Ceftriaxone	≤0.25	>32	73.4	26.6 (26.6)[c]
Ceftazidime	0.25	32	73.4	26.6 (26.6)[c]
Cefepime	≤0.12	>16	85.9	10.9
Imipenem	0.25	8	85.9	14.1
Levofloxacin	≤0.5	>4	76.6	23.4
Gentamicin	≤2	>8	84.4	10.9
Amikacin	1	32	89.1	1.6
Enterobacter spp. (59)				
Tigecycline	0.5	1	94.9	0.0
Piperacillin/tazobactam	4	64	79.7	8.5
Ceftriaxone	0.5	>32	72.9	25.6
Ceftazidime	≤1	32	78.0	22.0
Cefepime	≤0.12	2	94.9	3.4
Imipenem	0.5	1	93.2	0.0
Levofloxacin	≤0.5	≤0.5	94.9	5.1
Gentamicin	≤2	≤2	96.6	3.4
Amikacin	1	2	100.0	0.0
P. aeruginosa (83)				
Tigecycline	>4	>4	-	-
Piperacillin/tazobactam	8	>64	86.8	13.2
Ceftazidime	2	32	83.1	10.8
Imipenem	2	>8	85.5	13.3
Levofloxacin	≤0.5	>4	68.7	26.5
Tobramycin	0.5	1	92.8	4.8
Amikacin	2	16	95.2	3.6
Polymyxin B	1	1	100.0	0.0

a. According to CLSI (M100-S20-U) breakpoints except tigecycline, for which USA-FDA breakpoints were applied.
b. - = no breakpoint has been established by CLSI or USA-FDA.
c. Value in parenthesis indicates ESBL-phenotype rate (CLSI, 2010).
Abbreviations: TMP/SMX = trimethoprim/sulfamethoxazole; CoNS = coagulase-negative staphylococci.

- Tigecycline was highly active against *S. aureus* (MIC_{90}, 0.25 mg/L; 100.0% susceptible). Vancomycin and linezolid were also very active against this pathogen (100.0% susceptible), while 54.6, 35.2 and 13.0% of strains were resistant to oxacillin (MRSA), levofloxacin and clindamycin, respectively (Table 1).
- Tigecycline also exhibited good activity against other frequently isolated Gram-positive pathogens, including β-haemolytic streptococci (MIC_{90}, 0.06 mg/L; 100.0% susceptible), *Enterococcus* spp. (MIC_{90}, 0.25 mg/L; 98.6% susceptible), and coagulase-negative staphylococci (MIC_{90}, 0.25 mg/L; 100.0% susceptible).
- Linezolid and vancomycin were also very active against Gram-positive organisms, but generally eight- to 16-fold less potent than tigecycline (Table 1).
- ESBL-phenotype rates were 8.0 and 26.6% for *E. coli* and *Klebsiella* spp., respectively. Furthermore, 22.0% of *Enterobacter* spp. strains were resistant to ceftazidime (MIC, ≥16 mg/L) and 14.1% of *Klebsiella* spp. strains were resistant to imipenem (MIC, ≥4 mg/L; Table 1).
- Tigecycline was active against the most frequently isolated Gram-negative pathogens, including Enterobacteriaceae isolates with ESBL phenotypes and those resistant to imipenem. In contrast, tigecycline exhibited limited activity against *P. aeruginosa* (only less than 5% of cSSSI pathogens; Tables 1 and 2).
- Tigecycline and imipenem were the most active compounds tested against *E. coli* (MIC_{90}, 0.25 mg/L for both compounds), *Enterobacter* spp. (MIC_{90}, 1 mg/L for both compounds) and *Klebsiella* spp. (MIC_{90}, 1 mg/L and 8 mg/L, respectively) with 94.9-100.0% and 85.9-100.0% susceptibility rates, respectively. Amikacin was also very active against Enterobacteriaceae with susceptibility rates of 89.1-100.0% (Table 1).
- MRSA and VRE rates were 54.6 and 22.9%, respectively (Table 1), and tigecycline activity was not adversely affected by these resistance phenotypes (Table 2).

Table 2. Activity of tigecycline tested against 1,941 bacterial isolates causing cSSSI in USA medical centers (2009).

	Cumulative % inhibited at tigecycline MIC (mg/L) of:							
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4
S. aureus (1,165)	0.1	16.1	53.1	99.1	100.0			
MSSA (529)	0.2	14.9	52.9	100.0				
MRSA (636)		17.1	53.1	98.3	100.0			
β-haemolytic streptococci (212)	74.1	99.1	100.0					
Enterococcus spp. (140)	2.9	27.1	57.9	98.6	99.3	100.0		
Vancomycin-susceptible (108)	0.9	19.4	51.9	99.1	99.1	100.0		
Vancomycin-resistant (32)	9.4	53.1	78.1	96.9	100.0			
E. faecalis (98)	1.0	16.3	45.9	99.0	99.0	100.0		
E. faecium (36)	8.3	58.3	86.1	97.2	100.0			
CoNS (58)	5.2	37.9	65.5	96.6	100.0			
Viridans group streptococci (35)	68.6	85.7	97.1	100.0				
E. coli (125)	0.8	12.8	59.2	94.4	98.4	100.0		
Klebsiella spp. (64)			3.1	54.7	83.4	93.8	98.4	100.0
Enterobacter spp. (59)			1.7	37.3	79.7	93.2	94.9	100.0
P. aeruginosa (83)						3.6	8.4	44.6

CONCLUSIONS

- Tigecycline has provided a new class of antimicrobial agents to combat serious, resistant infections which continue to increase globally.
- This study demonstrates the continuing in vitro efficacy of tigecycline against isolates associated with cSSSI, including MRSA, VRE and multidrug-resistant Enterobacteriaceae.
- Continued monitoring of tigecycline activity on a global scale is needed to determine the overall role of this novel, broad-spectrum antimicrobial agent.